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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,078	11/08/2001	Donna T. Ward	RTS-0236	6940

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/007,078	WARD ET AL.	
	Examiner	Art Unit	
	J. D. Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *June 4, 2004 and August 6, and 13, 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-15,29 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-15,29 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8-13-2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 4, 2004 has been entered.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on August 13, 2004 was filed after the submission of the request for continued examination on August 6, 2004, and before the mailing of a non-final action. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner, and is enclosed herewith.

Status of Application/Amendment/Claims

Applicant's responses filed June 4, 2004 and August 13, 2004 have been considered. Rejections and/or objections not reiterated from the previous office action mailed February 6, 2004 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-15, 29, and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *Part of this rejection is directed to the entry of new matter, as explained below.*

The invention of the above claims is drawn to modified compounds 8 to 50 nucleobases in length targeted to EIF2C1 of SEQ ID NO: 3, wherein said modified compound hybridizes with and inhibits the expression of EIF2C1 by at least 42%, or 60%, or 80%. The invention is also drawn to internucleoside linkages, nucleobase, and sugar modifications, chimeras, and methods of using said modified compounds.

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Thus, an applicant complies with the written-description requirement by describing the invention, with all

its claimed limitations, and by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof.

To be clear, the claims submitted June 4, 2004 are considered to lack adequate support for the introduction of the term "modified compound" in claim 1, and thus this term is considered to constitute new matter. Furthermore, applicants are not considered to have adequately supported claims to the genera of 1) any modified compound that inhibits EIF2C1 of SEQ ID NO: 3 to the level of 42%, let alone 60% or 80% as recited in claims 1, 29, and 31 respectively, or 2) all compounds 8 to 50 nucleobases in length that target an active site of any EIF2C1 as recited in claim 11. The discussion for why these three elements are considered to lack adequate description is considered in order below.

The specification is considered to lack adequate description for the genus of all modified compounds that target EIF2C1 of SEQ ID NO: 3 as recited in claim 1, because applicants have not provided a definition of the term "modified", which is therefore given its plain meaning which is considered extraordinarily broad, encompassing significantly more than the molecules disclosed.

Applicants have not disclosed a sufficient number of structures that represent a full description of the breadth of this genus. Applicants have disclosed a number of antisense sequences that target and are perfectly complementary to SEQ ID NO: 3. Applicants have also

disclosed a list of possible nucleotide modifications that would fall within the scope of the term "modified". However, the term "modified" is considered to be much broader than mere nucleotide modifications. The term "modified", according to The American Heritage Dictionary of the English Language, (Fourth Edition Copyright © 2000 by Houghton Mifflin Company. Published by Houghton Mifflin Company.) means "To change in form or character; alter." Thus, the term "modified" is considered to add the "limitation" of alteration to the oligo without boundary, including not only structural modifications to each individual nucleotide, such as replacing any individual atom with another, but also changes to the sequence, among other things. Even taken conservatively, such language is considered to embrace virtually any sequence and compound so long as nucleobases are located somewhere within the molecule, including aptamers, PNA's, siRNA's, ribozymes, triplex forming oligos, nucleic acid/peptide conjugates, etc. Applicants simply are not considered to have adequately described a representative sample from such a genus of any possible modifications to oligos that target EIF2C1, let alone those that inhibit to the level of 42% as claimed instantly. One of skill could not envision the species contained within such a broad genus of modified compounds containing nucleobases, particularly based upon a specification which merely teaches antisense oligonucleotides that are perfectly complementary to their target. Applicants are not considered to have disclosed such breadth, and therefore the claims are rejected as containing new matter.

Applicants are also not considered to be in possession of the genus of all modified compounds that inhibit the expression of EIF2C1 of SEQ ID NO: 3 to the level of 42%, or 60% or 80% as recited in claims 1, 29, and 31 respectively,

The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. However, as stated in applicant's declaration under 37 CFR § 1.132 (submitted June 4, 2004, pages 3 and 4), "it is not currently possible to predict the level of inhibition of expression achieved against a particular gene with any particular oligomeric compound prior to carrying out the appropriate experiments. It is also not reasonable to expect for any particular gene or mRNA that any number of oligomeric compounds exhibiting at least 42% inhibition of expression, as stated in claim 1 of the present application, will be obtained." And further, "[T]his evidence demonstrates that one skilled in screening of oligomeric compounds cannot, *a priori*, reasonably expect a particular level of gene inhibition (i.e. such as at least 42%) of a gene or mRNA simply because methods of screening oligomeric compounds are available are/ or routine."

Applicants have described several examples of oligos that are capable of achieving target inhibition to the level of 42%. However, applicants have not described any sort of common structural feature(s) among such inhibitory oligos that impart the inhibitory function. Thus, while one of skill could envision the oligos disclosed in Table 1 of the specification, one of skill could not envision what it is about any other oligo that may or may not cause it to inhibit to the claimed level, and the specification is not considered to support claims to the genus of compounds inhibiting EIF2C1 to the level of 42%.

Finally, applicants are not considered to be in possession of the genus of any compounds 8 to 50 nucleobases in length that target an active site of any EIF2C1 as recited in claim 11.

It is noted that the rejected claim does not recite any sequence identifier. The genus of EIF2C1 targets is therefore considered to be defined and claimed by its function rather than by

any specific or particular structure. Accordingly such language embraces any sequence of any EIF2C1, or any such molecule with analogous EIF2C1 activity, known or yet to be discovered, along with any isoform or allele or any variant that is within reasonable similarity to this family of proteins that retains EIF2C1 function.

The only full length EIF2C1 sequence taught in the specification is SEQ ID NO: 3. While the specification refers a partial genomic sequence of EIF2C1, the sequence of SEQ ID NO: 3 is the only support provided for the full length EIF2C1. The presence of only one full length sequence of EIF2C1 is not considered to meet the requirements for disclosure of a representative sample of structures that correlate to the genus of any molecule encompassing any EIF2C1 activity. While the claims are drawn to nucleotide inhibitors of said EIF2C1, one of skill would understand that knowledge of the sequence of the target is required for inhibition of said target. Because applicants are not considered to be in possession of the genus of targets, applicants are also not considered to be in possession of inhibitors of said genus of targets. This is particularly true in view of the fact that EIF2C1 is a transcription factor, and since transcription factors tend to be widely conserved throughout the animal kingdom, one of skill would consider this to be a broad genus. One of skill would not recognize from the specification or the prior art that applicants were in possession of the instantly claimed genus of any nucleic acid inhibitor of any EIF2C1 target encompassing known or undiscovered EIF2C1 transcription factors based upon the disclosure of one sequence.

Response to Claim Rejections - 35 USC § 102/103

Claims 1, 2, 12 and 14 are rejected under 35 U.S.C. 102(b) and 103(a) as being anticipated and/or obvious by Koesters et al. (of record) and claims 1, 2, 12 and 14 are also rejected under 35 U.S.C. 102(e) and 103(a) as being anticipated and/or obvious by Schalling et al. (U.S. Patent Number 5,695,933), for the same reasons of record as set forth in the Office actin mailed August 25, 2003.

Applicants have argued that the amended claims, which now recite the limitation that the subject compound be "modified", are free of the prior art because neither the oligo of Koesters *et al.* nor that of Schalling *et al.* are modified. However, the term "modified" is considered to be relative term, since as described above its plain meaning is "altered". Since there is no indication in the specification as to the limits of what constitutes a "modified" compound, or what the compound is altered in comparison to, and due to the substantial breadth of such a term, both of these oligos are considered to be modified, for example, as compared to their precursors formed during the process of synthesis. Therefore, the claims stand rejected because the term "modified" is not considered to be sufficient to free the claims from the prior art.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4-15, 20, 24 and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koesters et al., in view of Cikaluk et al. (Mol. Biol. Cell, 1999. v10:3357-3372), Taylor et al., Baracchini et al., and Milner et al.

Applicants have traversed by asserting that the Office action identifies no motivating force that would impel one of ordinary skill to modify the respective teachings to achieve the claimed invention.

This assertion is made in spite of the fact that antisense inhibition is a well known and well practiced technique used in the inhibition of specific gene expression (as evidenced by Taylor and Baracchini and Milner), that the sequence of applicants instant target is known and, further, is considered an interesting candidate for potential involvement in Wilms tumorigenesis (Koesters), and finally, that the *C. elegans* homologue of the instant target was inhibited by a nucleic acid based inhibitor (Cikaluk).

Applicants have attacked the cited motivation from Koesters *et al.*, who indicates that EIF2C1 is considered an interesting candidate for potential involvement in Wilms tumorigenesis, by saying that the reference, although providing motivation for further experimentation, is only general, and therefore is not the required motivating force needed to reach the instant invention, because it does not indicate that antisense is a preferred mechanism for inhibition. This is not convincing, because antisense inhibition is a well-known and well-practiced technique as evidenced by Taylor, Baracchini and Milner, (cited in the instant rejection) as well as over 250 patents issued to date to the instant assignee. Indeed, the first paragraph Taylor *et al.* states: "Antisense technology provides an elegant and simple approach to inhibiting the expression of a target gene. Antisense oligonucleotides (ONs) are short sequences (7-30 nucleotides of nucleic acids that bind to a specific region of a target messenger RNA (mRNA) according to Watson-Crick base pairing rules (Fig. 1) and can be designed to inhibit any gene target provided that the sequence is known. The specificity and ease of design of ONs make them attractive candidates as therapeutic agents and as research tools for the elucidation of gene function." Thus, clearly antisense is considered an attractive option for anybody seeking to inhibit the expression of a target gene, which applicants concede there is general motivation to do.

Regarding whether the motivation provided by Koesters or Cikaluk, applicants arguments that the motivation is not "impelling" is not considered convincing, because the cited combination suggests that "an elegant and simple approach to inhibiting the expression of a target gene... and can be designed to inhibit any gene target provided that the sequence is known"; since the sequence is known and is considered "an interesting candidate for potential involvement in Wilms tumorigenesis" (i.e. the instant EIF2C1 target), applicants position that there is no specific motivation is unconvincing.

Applicants also assert that the present combination raises only an inappropriate "obvious to try" standard. Applicants argue that Milner cannot support a reasonable expectation of success because Milner does not establish that one can obtain compounds that one of ordinary skill would obtain compounds that inhibit by at least 42%. In support applicants cite a passage from Milner, which, states that variable success can be expected from the use of any individual antisense oligo. In response, applicants are reminded that the instant claims are not drawn to any individual oligo, but rather to the genus of any oligo that hybridizes to and inhibits EIF2C1 of SEQ ID NO: 3. Therefore, applicants must establish that there is no reasonable expectation of finding any oligo that inhibits the target. Milner does not teach that one would not be expected to find any oligo capable of inhibiting its target. To the contrary, Milner teaches a high throughput screening method that one of ordinary skill would be able to practice and subsequently identify such oligos. Milner provides a detailed comparison of a number of different oligos that inhibit 50% (see table 1) and determines the concentration necessary to attain such inhibition.

Furthermore, such functional language is not accorded much patentable weight in a compound claim when the compound itself is considered to be taught by the prior art (see M.P.E.P. 2114, for example).

Applicant' reliance on functional language to clear the claims from the prior art is confounded by the fact that no particular conditions under which inhibition is to be measured have been claimed. Because hybridization, upon which antisense inhibition is dependent, is itself dependent upon such factors as temperature, salinity, and the presence of RNA binding proteins, among other things, the failure to claim specific conditions under which the 42% inhibition is achieved provides substantial breadth under which one could reasonably expect to find an oligo that inhibits to the requisite degree. It is maintained that one of ordinary skill, by manipulating conditions of temperature, salinity of concentration, could greatly increase the number of oligos that return results to the claimed degree.

Applicants have provided a declaration under 37 CFR § 1.132. The declaration includes a statement from a representative of the assignee indicating her belief that it is never possible to predict reliably before the screen is performed, whether a particular level of gene inhibition will be reached. However, over 259 U. S. Patents have been issued to the instant assignee, and after reviewing table 1 from 15 of them, it was found that every single one of these demonstrated inhibition of at least 42%. Even applicants own declaration reports results whereby inhibition of 50% against one gene, and 40% against the other was obtained.

This is particularly noteworthy since applicants have not indicated whether these examples are considered to be representative of the results of such tests against any gene, or whether alternatively, they comprise the results from two genes for which applicants are having a

difficult time finding oligos that inhibit to a specified level. In further detail from the 15 U. S. Patents referred to above, tables of antisense oligo inhibition assays from two randomly selected patents (the first two patents that resulted from a search for those with the term "antisense" in the claims) show that one could reasonably expect to screen a reasonable number of oligos and find at least a few capable of significant levels of target inhibition. For example, table 1 of U. S. Patent Number 6,001,992 (col. 27) contains tests results for 15 oligos, with 4 of the 15 exhibiting over 60% inhibition. Thus, the inventors of patent found 1 oligo exhibiting 60% inhibition for every 3.6 screened, well within the range indicated by Taylor et al. A table from the other randomly selected different patent, U. S. Patent Number 6,312,900 (col. 21) returned a much higher number of hits, whereby 7 out of 10 oligos tested achieved inhibition of at least 60%. This is 1 oligo for every 1.4 tested that achieve said level of inhibition. Thus, a strong case can thus be made that applicants' submitted data may not be representative of every instance of antisense oligonucleotide mediated gene inhibition. These citations do not constitute a new grounds of rejection, but are merely provided to rebut applicants arguments and declaration.

Second, applicants have not established whether the assays provided in the declaration fall within the conditions taught by the instant combination of prior art. For example, Taylor et al. teaches that in order to achieve this inhibition, high affinity chimeras must be used. While applicants have certainly used chimeric oligos comprising DNA and RNA, these do not appear to be high affinity chimeras, that is those that contain modifications designed to increase hybridization affinity. Applicants have not indicated either way what their conditions are relative to the instant teachings, and thus it is not clear how such evidence is related to the instant rejection, let alone defeats it.

Third, even if applicants were to clearly establish that the instant references are wrong, and that one of ordinary skill would need to screen more than 3-6 oligos using modern bioinformatics and high affinity chimeras to find an oligo that inhibits at least 66%, an assertion that is not adopted by the examiner, applicants have simply not provided convincing evidence that the number of oligos that would have to be screened would result in no reasonable expectation of success. One of ordinary skill in the art practicing the methods known in the art and set forth, for example by Baracchini, Milner, and Taylor would be reasonably assured of finding among the 70 at least one oligo that inhibits its respective target to the claimed degree of 42 %, and probably much more in view of the results from the randomly found antisense patents cited above. In this case, applicants merely assert that one cannot assert *a priori* whether a particular oligo would inhibit its target to the requisite degree, and that one of ordinary skill would require screening more than 3-6 oligos. If applicants are suggesting that the state of the art is so unpredictable that one of ordinary skill might try every conceivable oligo directed against a specific target *in vitro* and never achieve the requisite level of inhibition, which they have not done, applicants are invited to clearly state such an assertion on the record, and provide evidence in support of such an assertion. In the absence of this, it is maintained that Taylor, and the state of the art of using antisense *in vitro* in general is considered to be enabled.

Conclusion

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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